UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/894,547	06/28/2001	William R. Wagner	214001-00810-1	6231

7590 08/08/2006

Debra Z. Anderson
Eckert Seamans Cherin & Mellott, LLC
44th Floor
600 Grant Street
Pittsburgh, PA 15219

EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/894,547	WAGNER ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-29* is/are pending in the application.

4a) Of the above claim(s) *6,13-18,21-23,25 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7-12,19,20,24 and 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

2. Claim 4 has been cancelled. Claims 6, 14-18, 21, and 22 have been withdrawn. Claims 1, 3, 5, and 11 have been amended. No new matter was introduced by these amendments.

Newly submitted claims 23, 25, and 29 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the new claims 23 and 25 introduce new limitations that require a distinct search from the search required for the originally presented invention. For example claims 23 and 25 are drawn to a method that uses different compositions, such as different reactive groups on the target tissue or different biological entity to be delivered to the target tissue.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 23, 25, and 29 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1-3, 5, 7-12, 19, 20, 24, and 26-28 are under examination.

Response to Arguments

3. Claims 1-3, 5, 7-12, 19, 20, 24, and 26-28 remain rejected under 35 U.S.C. 112, first paragraph for failing to comply with the enablement requirement for the reasons set forth in the previous Office Action. Applicant's arguments filed 05/24/2006 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that **(i)** tissue and cell surfaces contain molecules that can be easily modified and therefore, the different mechanisms of action are not of concern as long as the clinician selects a suitable signaling molecule that is recognized by the tissue modified such that it comprises the recognition molecule, **(ii)** that Garnett is a 2001 publication and therefore it is not prior, **(iii)** even if Garnet could be used as art, citing Garnet misconstrues the scope of the instant invention because, in Applicant's opinion Garnett citation pertains only to the delivery of macomolecular drugs and this does not necessarily apply to other forms of drugs. Therefore, Applicant asserts, the disclosure is enabling for the delivery to a certain tissue/cellular surface and a person of skill in the art would know to use the prior art to select a suitable combination, **(iv)** the invention entails for specific delivery of a chemical/biological entity and therefore specific binding using a suitable system, **(v)** Hoya is not prior art and even if it were, Hoya teaches one example of intravascular delivery and therefore the Examiner, by citing Hoya, acknowledges that that specific binding and delivery is possible using Hoya's technique. Moreover, Applicant argues, the specification does not need how to make and use every possible variant of the claimed invention, **(v)** Hamblett is not prior art and even if it were, one of skill in the art

would have known how to solve the problem because that the prior art teaches adding an excess of the targeted agent or using a particulate carrier that has a great amount of targeting entity, and **(vi)** even if the specification disclose only two working examples, the Examiner has failed to take into the account the teachings of the prior art regarding suitable signaling/recognition pairs. Applicant argues that the focus of the instant invention is the targeted delivery and not which signaling/recognition system would prove successful and therefore, the specification does not need to describe how to make and use every possible variant because the artisan's knowledge of the prior art and routine experimentation can fill the gaps. Accordingly, Applicant requests the withdrawal of the rejection.

First, contrary to Applicant arguments, the art cited under enablement rejection does not need to be prior art because the intent is to demonstrate that the invention is not enabled due to the unpredictability of the art at and even after the time the invention was made.

Second, as stated in the previous Office Action, the Examiner acknowledges that the invention is enabled for a method of two-step delivery of a chemical or biological entity to an isolated vascular tissue (either *in vitro* or *in situ*) and not for a method for the delivery to any target tissue or cellular surface of a patient (which includes *in vivo*), as broadly claimed. Applicant claims delivery to a certain target tissue/cell surface. Applicant argues that the invention entails for specific delivery of a chemical/biological entity and therefore specific binding using a suitable system. However, the instant method does not rely on any inherent feature present on the targeted surface and

therefore the delivery cannot be specific unless the targeted tissue/cell surface is not isolated. Hoya reference was cited only to demonstrate the requirement of isolating the target tissue for specific delivery to the target cell via the claimed method. Hoya teaches that intravascular delivery using endothelial biotinylation and subsequent avidin binding targeted is feasible, as long as the blood flow is completely blocked and the vessels are completely flushed with saline before avidin binding. Therefore, even if one of skill in the art would be able to select a suitable pair of signaling/recognition molecules, one of skill in the art would not be able to specifically deliver the chemical or biological entity to the target tissue via the instant method in a patient as broadly claimed. Hence, the scope of enablement of delivery to isolated vascular tissue.

Third, Applicant asserts that Garnett reference teaches only the delivery of macromolecular drugs and therefore Garnett's teachings do not apply to other forms of drugs. However, it is noted that Garnet teaches macromolecular conjugates and drugs in any form conjugated to strepatavidin/avidin are macromolecular conjugates. Regarding the avidin/biotin system and the argument that one of skill in the art would know how to solve the problem posed by the presence of serum biotin (See Hamblett et al. reference) because the prior art teaches adding an excess of targeted agent or using a particulate carrier that has a great amount of targeting activity, the Examiner disagrees. Clearly the post-filing art teaches that problems with the endogenous biotin blocking the biotin-binding sites of streptavidin are still an issue and that strategies to overcome them must be developed. Moreover, the specification does not teach any

strategy to block the endogenous biotin. Therefore, one of skill in the art would require undue experimentation to know how to achieve effective blocking of endogenous biotin. The examiner acknowledges that signaling/recognition molecule pairs are well known in the art. However, the claimed invention is a method of specific delivery of a chemical/biological entity and therefore targeting to the desired tissue/cell surface is essential for the instant invention. It is noted that problems with the use of any signaling/recognition molecule pair for specific delivery *in vivo* exits. The specification fails to teach the use of any signaling/recognition system for specific delivery to any tissue/cell surface in a patient and therefore provides enough of a disclosure to allow for one of skill in the art to use the method to deliver a chemical or a biological entity to an isolated vascular tissue, wherein the blood flow is blocked and the blood is removed by flushing before the use of the desired signaling/recognition molecule system.

4. Claims 1, 2, and 7-9 remain rejected under 35 U.S.C. 112, first paragraph for failing to comply with the enablement requirement for the reasons set forth in the previous Office Action. Applicant's arguments filed 05/24/2006 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that, although the Applicant agrees with the Examiner interpretation, one of skill in the art would know that the reference to N-hydroxy-succinimide (NHS) as the reactive group entails the use of NHS ester of biotin, because, as the Examiner indicated, the ester form of biotin is

described in the prior art. Therefore, Applicant asserts that the claims are enabled under 35 U.S.C. 112.

Contrary to Applicant's arguments, since the claim recites the use of NHS as the reactive group and the art does not teach the use of NHS *per se* (see the previous Office Action), it does not matter whether one of skill in the art would recognize that Applicant meant NHS-biotin. The invention, as claimed, is not enabled.

Claim Rejections - 35 USC § 102

5. Claims 1, 10-12, 20, and 24 remain rejected under 35 U.S.C. 102(b) as being anticipated by Saga et al. (Cancer Research, 1994, 54: 2160-2165), for the reasons set forth in the previous Office Action. Applicant's arguments filed 05/24/2006 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that, since claim 4 is not rejected by Saga et al., including all its limitations in claim 1 should overcome the rejection.

It is noted that claim 4 was not included in the instant rejection because the Applicant elected covalent binding as species from the species recited in claim 4 and Saga et al. do not teach covalent binding. However, as amended, claim 1 now recites "ionically, covalently, non-covalently or hydrogen bonding". Since Saga et al. teach non-covalent binding, the instant rejection is maintained (see the previous Office Action).

6. Claims 1, 5, 7, 9-11,19, 24, and 28 remain rejected under 35 U.S.C. 102(a) as being anticipated by Wojda et al. (Bioconjugate Chem, 1999, 10: 1044-1050), for the reasons set forth in the previous Office Action. Applicant's arguments filed 05/24/2006 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that Wojda et al. disclose a method of delivering biotin conjugates to the nucleus of cells and it does not target a specific cell or tissue. Applicant argues that, in contrast, claim 1 recites a method for the delivery of a chemical or a biological entity to a tissue or cellular surface by attaching the entity to the target via interaction with a recognition molecule, and this is a method for direct delivery, not endocytotic delivery. Applicant continues arguing that Wojda et al. disclose only the avidin/biotin system, whereas the Applicant's invention uses any suitable signaling/recognition system.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the method is not endocytic delivery) are not recited in the rejected claim(s). And even if they were, contrary to Applicant's arguments, Wojda et al. do teach a method of delivery to a cell surface of a chemical and pharmaceutical entity because, in order to be endocytosed, the chemical entity must first specifically bind to the surface of the cell that was biotinylated, i.e., Wojda et al. teach a method of direct delivery to the target cell. Moreover, the Applicant claims an entire genus of signaling/recognition systems that is anticipated by the avidin/biotin system of Wojda et al.

Claim Rejections - 35 USC § 103

7. Claims 1, 2, 8, 10-12, 20, and 24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Saga et al., in view of both Francis et al. (International Journal of Hematology, 1998, 68: 1-18) and Kaiser et al. (Bioconjugate Chem, 1997, 8: 545-551) for the reasons set forth in the previous Office Action. Applicant's arguments filed 05/24/2006 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that, since claim 4 is not rejected by Saga et al., including all its limitations in claim 1 should overcome the rejection. It is noted that claim 4 was not included in the instant rejection because the Applicant elected covalent binding as species from the species recited in claim 4 and Saga et al. do not teach covalent binding. However, as amended, claim 1 now recites "ionically, covalently, non-covalently or hydrogen bonding". Since Saga et al. teach non-covalent binding, the instant rejection is maintained (see the previous Office Action).

8. Claims 1,10-12, 19, 20, and 24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Saga et al., in view of both Chinol et al. (British Journal of Hematology, 1998, 78: 189-197) and Wilbur et al. (Bioconjugate Chemistry, 1996, 7: 689-702) for the reasons set forth in the previous Office Action. Applicant's arguments filed 05/24/2006 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that, since claim 4 is not rejected by Saga et al., including all its limitations in claim 1 should overcome the

rejection. It is noted that claim 4 was not included in the instant rejection because the Applicant elected covalent binding as species from the species recited in claim 4 and Saga et al. do not teach covalent binding. However, as amended, claim 1 now recites "ionically, covalently, non-covalently or hydrogen bonding". Since Saga et al. teach non-covalent binding, the instant rejection is maintained (see the previous Office Action).

9. Claims 1,3, 10-12, 20, and 24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Saga et al., in view of Muzykantov et al (Proc Natl Acad Sci USA, 1999, 96: 2379-2384) for the reasons set forth in the previous Office Action. Applicant's arguments filed 05/24/2006 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that, since claim 4 is not rejected by Saga et al., including all its limitations in claim 1 should overcome the rejection. It is noted that claim 4 was not included in the instant rejection because the Applicant elected covalent binding as species from the species recited in claim 4 and Saga et al. do not teach covalent binding. However, as amended, claim 1 now recites "ionically, covalently, non-covalently or hydrogen bonding". Since Saga et al. teach non-covalent binding, the instant rejection is maintained (see the previous Office Action).

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa

Janet L. Epps-Ford
Primary Examiner
Art Unit 1633